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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/657,276	09/07/2000	Dominique P. Bridon	REDC-2111 USA	9972

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EXAMINER	
SNEDDEN, SHERIDAN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/657,276	BRIDON ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9,11,12 and 14* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9,11,12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. This Office Action is in response to Paper filed 2 December 2003. Applicant's amendment of claims 7, 8, and 9 is acknowledged. Claims 7-9, 11-12 and 14 are under pending.

Withdrawal of Objections and Rejections

2. The objections and/or rejections not explicitly restated or stated below are withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9, 11-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty *et al.* (US 6,103,223) in view of Brenton *et al.*

Pouletty *et al.* teach a method for protecting a therapeutic peptide that is sensitive to peptidase degradation in vivo. The method involves preparing a composition in which first and second components are provided. The first component is administered to a mammalian host into blood for covalent bonding to a second blood component, where the components have an extended lifetime in the blood stream. The first component comprises an active functionality and an agent of interest or a first binding entity. A second component may be subsequently administered to the patient, which comprises a second binding entity, complementary to the first

binding entity and an agent of interest. By virtue of binding to long-lived blood components, the half-life of the agent of interest is greatly extended in vivo. The first compound will comprise the active functionality, a linking group, and the agent of interest or first binding entity.

The functionalities which are available on proteins are primarily amino groups, carboxyl groups and thiol groups. While any of these may be used as the target of the reactive functionality, for the most part, bonds to amino groups will be employed, particularly formation of amide bonds. To form amide bonds, one may use a wide variety of active carboxyl groups, particularly esters, where the hydroxyl moiety is physiologically acceptable at the levels required. While a number of different hydroxyl groups may be employed, the most convenient will be N-hydroxysuccinimide, and N-hydroxy sulfosuccinimide. As the first component may be active proteins, regions of differing therapeutic activity is inherent. Serum albumin is disclosed as a long-lived blood associated second component. The anchor is disclosed as comprising N-hydroxy succinimide ester (regarding claim 11). The conjugate may be administered in vivo or ex vivo.

Pouletty *et al.* disclosed a method of analyzing the peptide-blood component for increased half-life. Pouletty *et al.* does not expressly teach the added step in analyzing the peptide blood component for resistance to peptidase degradation.

Brenton *et al.* teach that the conjugation of a peptide to albumin protects the conjugate from peptidase degradation that results in the increased half-life.

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform the analyzing step of the peptide blood component for resistance to peptidase degradation. Analyzing the peptide blood component for resistance to peptidase

degradation is an alternative method to determine the increased half-life of an albumin conjugate, and a person of ordinary skill in the art would have been motivated to perform the analysis in order to determine if the conjugate resulted in a composition that had an increase half-life over the active peptide alone. The person of ordinary skill in the art would have expected success in finding a compound of increased half-life having analysis the conjugate for resistance to peptidase degradation. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

4. Applicant argues that Pouletty *et al.* do no teach or suggest protecting a therapeutic peptide from peptidase degradation (page 7 of the response). Applicant argues that Pouletty *et al.* created the albumin conjugate in order to 1) bind undesirable entities circulating in the blood, or 2) to extend the half life of the compound. Applicant argues that Pouletty does not teach protection from peptidase degradation and, as a result, could not teach a step analyzing the stability of an albumin conjugate towards peptidase degradation (page 8 of the response). Applicant further notes that Pouletty *et al.* fail to disclose any criterion for determining the position of the attachment of the compound to the anchor, which is interpreted to mean albumin (Response at page 8, line 6).

Applicant argues that Brenton teach a chemically modified, non-native albumin conjugated to a 411 amino acid peptide. Applicant implies that the albumin of Brenton *et al.* would not be correctly folded and non-functional.

At page 11 of the response, Applicant argues that the claims are directed to affirmative method steps that are not inherent in the teaching of Pouletty *et al.* The affirmative step is

"analyzing the stability of said peptide albumin conjugate has a higher stability than the unconjugated therapeutic peptide." Applicant argues that this step is not taught and not inherent to the teachings of Pouletty *et al.* or Brenton *et al.*

5. Applicant's arguments have been fully considered but they are not persuasive. It is first noted that the Applicant raised arguments against the references individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Here, Pouletty *et al.* teach the peptide albumin conjugate of the claimed method (and/or method of making product). With regards to the product, Applicant argued that Pouletty *et al.* fail to disclose any criterion for determining the position of the attachment of the compound to the anchor. This argument is unpersuasive as claim 7 requires that placement of the anchor to be at the C-termunis, N-terminus, or anywhere between (see 7(a)). Thus, any argument that the claim requires a precise positioning of the anchor is unpersuasive.

Applicant's only notable contention to the patentable novelty of the claimed method is that the additional step of analyzing the stability of a peptide albumin conjugate for higher

stability as compared to the unconjugated therapeutic peptide would distinguish the claimed method from the teaching of Pouletty *et al.* Here, Pouletty *et al.* does teach that the half-life of the conjugate is increased when compared therapeutic peptide alone. Increased half-life is a measure of the stability of a peptide, where greater half-life would mean greater stability. Applicant's arguments imply that the increased half-life of the Pouletty conjugates are a result of reduced elimination of the conjugates and not a result of any resistance to peptidase degradation. This is unconvincing as any increased half-life would necessarily involve an element of increased resistance to peptidase degradation.

This element of increased resistance to peptidase degradation was clearly established in the teachings of Brenton *et al.* Brenton *et al.* was concerned with preventing the formation of urokinase from pro-urokinase that result from a peptidase working on pro-urokinase. In order to prevent this peptidase degradation, Brenton formed a pro-urokinase/albumin conjugate that resulted in the increase half-life of the therapeutic peptide. Brenton was mimicking a natural process in order to position the albumin in a way that would not interefere with the activity of pro-urokinase. Applicant argued that pro-urokinase is greater than 50 amino acids and thus irrelevant. However, Brenton *et al.* teach the natural function of albumin to protect peptides from peptidase degradation that is analyzed or measured in half-life. Thus, the analysis step that Applicant contends is novel, is taught by the combined references.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., chemically modified, non-native albumin) are not recited in the rejected claim(s). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for regular communications to the organization where this application or proceeding is assigned is (703) 746-3975.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
April 4, 2004
SKS

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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